THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 305 East 45th Street, New York 17, New York

Vol. 3, No. 26 (Issue #77) December 22, 1961

LIBRIUM IN ALCOHOLISM

Chlordiazepoxide (Librium — Roche) is being promoted as the drug of choice in the management of the hyperactivity and agitation of acute alcoholism and as an adjunct to psychotherapy in the rehabilitation period of chronic alcoholism. Paraldehyde, barbiturates, chloral hydrate, chlorpromazine (and other phenothiazines) have been successfully used to control the agitation, delirium tremens and hallucinations of the acute alcoholic brain syndrome; published reports indicate that Librium is also effective.

Like other sedative-tranquilizer drugs, Librium does not shorten the period of delusion or hallucination but it does reduce the patient's anxiety reaction to these symptoms. Despite the claims made for the drug, controlled trials and much more extensive clinical experience are required before it can be asserted that Librium is superior to older sedative-tranquilizer drugs for the management of the acute alcoholic brain syndrome. All of the drugs are central-nervous-system depressants; when intravenous administration is required, it should be done with great caution because of the danger of severe or even fatal respiratory depression.

CHRONIC ALCOHOLISM - Several authors have reported that Librium increases the effectiveness of psychotherapy in the chronic alcoholic patient, but none of these favorable studies were properly controlled, and none evaluated its effects over sufficiently long periods. In one well-controlled trial, Librium was no more effective than a placebo in altering the "natural course of events" of chronic alcoholism (H. B. Mooney, et al., Dis. Nerv. Sys., 22:Section 2:44, July 1961).

Sedatives and tranquilizers are sometimes useful in the management of chronic alcoholism, but only as a temporary measure. For such use, the phenothiazines have the advantage of causing less clouding of the sensorium than barbiturates, and the same advantage is claimed for Librium. Medical Letter consultants are not convinced of either the effectiveness or the safety of any sedative or tranquilizing drug for long-term management of chronic alcoholism. The phenothiazines, unlike other drugs, are not addicting, but the frequency and the severity of their toxic effects make it difficult to justify their use in chronic alcoholism.

ADDICTION HAZARD - As with many other drugs, the regular use of Librium in chronic alcoholism may result in the substitution of a new addiction for an

old one, particularly since the prescribed doses are certain to be exceeded by some patients. Despite the fact that the manufacturer's promotion literature contains a warning regarding addiction-prone individuals, it still advocates the use of Librium in chronic alcoholism. While the toxic effects of Librium appear to be less severe than those of the phenothiazines, there are reports of hypotension, extrapyramidal disturbance, pretibial edema, rashes, and decreased libido. Confusion resembling drunkenness has also been reported (F. Lemere, JAMA, 174:893, 1960), as well as convulsions and other withdrawal symptoms after abrupt cessation of treatment with large doses (L. E. Hollister, et al., Psychopharmacologia, 2:63, 1961).

In short, while Librium is a useful drug for the relief of the syndrome of acute alcoholism, its superiority to other sedative and tranquilizing drugs has not been established. And there is as yet no evidence that Librium or any other sedative or tranquilizing drug can safely and favorably influence the course of chronic alcoholism. Group or individual psychotherapy is often helpful; regular participation in the program of Alcoholics Anonymous is probably the most effective long-term measure.

NEW DRUGS AND TECHNIQUES FOR CANCER. II.

This is the second in a series of reviews of chemotherapeutic agents used in the treatment of malignant tumors. The first (The Medical Letter, 3:77, 1961) considered the alkylating agents. Most of the drugs and techniques discussed in the present review are still in the investigational stage. The choice by a physician of an anticancer drug for a patient is not easy, in view of rapid developments in screening and experimental trial of such agents. He can usually get help from tumor boards of major hospitals, particularly those associated with medical schools, as well as from special cancer research institutions and hospitals. Government grants have been made to many hospitals for the free care (including travel expenses) of patients with cancer, as well as certain other serious diseases, who are willing to accept the requirement of experimental trial of chemotherapeutic agents.

ANTIBIOTICS - Actinomycin D (Merck) - Of the several actinomycins tried in cancer patients, only Actinomycin D is currently available for experimental clinical use. It has been most effective for certain childhood tumors, particularly Wilm's tumor with pulmonary metastases; and it has been useful in some instances of choriocarcinoma resistant to methotrexate. In combination with chlorambucil and methotrexate, Actinomycin D has produced remissions of certain testicular tumors (see below). When given simultaneously with local irradiation, it has also been found useful as a tissue sensitizer in some types of cancer. In excessive doses, severe toxic effects may develop rapidly; these include painful cheilosis and glossitis, oral ulceration, and bone-marrow depression. Mitomycin C is another antibiotic available only for experimental trial. It has an occasional effect against Hodgkin's disease and ovarian cancer.

ANTIMETABOLITES - Methotrexate, USP (Lederle) — formerly called amethopterin — not only has a well established effect in the palliation of acute leuke-

mia in children, but it has also proved valuable in treating metastatic choriocarcinoma in women (it is much less effective against choriocarcinoma in men). Seemingly complete remissions of widespread metastases have been obtained for as long as five years in about 40 per cent of the female patients. Courses of methotrexate are best given orally in doses of 15 to 25 mg. daily for a period of five days, and repeated until tumor response or toxicity occurs (bone-marrow depression, oral ulceration or bleeding, and impaired renal function).

The use of Actinomycin D in combination with chlorambucil and methotrexate in the management of choriocarcinoma and embryonal cell carcinoma of the testes has resulted in remission rates of 35 per cent, with prolonged disappearance of metastases in about 6 per cent of the patients.

PURINE ANTAGONISTS - 6-Mercaptopurine, USP (6MP; Purinethol — Burroughs Wellcome). Although this is the most useful drug available for acute leukemias in adults, it is ineffective against the solid cancers, as well as against lymphomas, and chronic lymphocytic leukemia.

PYRIMIDINE ANTAGONISTS - 5-Fluorouracil and 5-Fluorodeoxyuridine (5FU and 5FUDR — Roche) are recent additions to experimental anticancer drug resources. The former is much cheaper and more readily available. (For a comprehensive review of the indications, doses and toxicity of these drugs, see R. R. Ellison, Med. Clin. N.A., 45:677, May 1961.) With 5FU, significant tumor regression has been observed in metastatic breast cancer, and to a lesser extent in gastrointestinal-tract malignancy. Patients who do not respond to hormone treatment of metastatic breast lesions may respond to alkylating chemicals or to 5FU.

The usual dosage schedule for 5FU is 15 mg./kg. of ideal weight, given intravenously each day for three or four days; then half to two thirds of this dose is given every other day if toxicity does not develop. Extreme caution in administration is required since toxic reactions to 5FU (and 5FUDR) may be abrupt and severe, consisting of vomiting, bloody diarrhea, severe depression of the bone marrow, and painful ulcerations of the oral cavity. Serious toxic symptoms, sometimes fatal, may not appear until eight days after the last dose (C. G. Zubrod, JAMA, 178:832, 1961).

VINBLASTINE SULFATE (Velban — Lilly), an alkaloid derived from the periwinkle plant (Vinca rosea), is currently undergoing clinical evaluation. It has been used with some success against cases of Hodgkin's disease refractory to irradiation and alkylating agents, and significant effects have also been reported in solid cancers, as well as against acute monocytic leukemia. However, one Medical Letter consultant failed to observe significant remissions of solid cancers even when the drug was given at toxic levels.

o, p'DDD (2, 2-bis[4-chlorophenyl, 2-chlorophenyl]1, 1-dichloroethane) - Medical Letter consultants have confirmed the value of this oral agent (available as yet for experimental trial only) in causing regression of lesions in patients with hyperfunctioning adrenal cortical cancer. The toxicity of o, p'DDD is relatively mild (D. M. Bergenstal, et al., Ann. Int. Med., 53:672, 1960).

TREATMENT OF MALIGNANT EFFUSIONS - Injections of Thio-TEPA and nitrogen mustard into the pleural or peritoneal space have been found effective in the management of effusions. To control recurrent effusions, a single dose of about half of the recommended initial systemic course is used after removal of as much effusion fluid as possible.

WOUND IRRIGATION WITH ANTICANCER CHEMICALS - Investigational studies are still too limited to permit judgment of the effectiveness of dilute solutions of nitrogen mustard or of such antiseptic agents as Dakin's solution, employed during surgery, in controlling the recurrence rate of cancer in man.

INFUSION AND PERFUSION - Both perfusion and intra-arterial infusion permit the use of large doses of short-acting drugs, and provide high drug concentrations locally with relatively little systemic toxicity. Although the addition of drug antagonists [such as citrovorum factor (Leucovorin — Lederle)] to the systemic circuit has added to the safety of these methods, their effectiveness is still limited by the inadequacies of all anticancer drugs.

ADJUVANT CHEMOTHERAPY - Surgeons are studying the value of giving systemic anticancer drugs at the time of operation, when the smallest number of residual tumor cells are likely to be left in the body, and before any circulating cells can become established as metastatic tumors. The results of cooperative trials in gastric cancer treated with Thio-TEPA and lung and colon cancers treated with nitrogen mustard have unfortunately been unpromising. The use of Thio-TEPA as an adjuvant to breast cancer surgery, however, is reported to be more encouraging.

TORECAN

Thiethylperazine maleate (Torecan — Sandoz) is a piperazine phenothiazine newly promoted as "an extremely effective antiemetic in a large number of clinical conditions." It is claimed to have a greater effect on the vomiting center than other phenothiazines. Whether or not this claim is correct, the published clinical trials do not show that the drug has greater effectiveness than such antiemetics as barbiturates, antihistamines and chlorpromazine (see The Medical Letter, 3:50, 1961 for a review of antiemetics).

USE IN VERTIGO - Torecan is claimed to reach a relatively high concentration in the cerebellum, and the manufacturer states that this may explain the effectiveness of the drug against vertigo. The only support for an effect on vertigo in man, however, is found in two uncontrolled clinical reports — hardly acceptable evidence, especially in a condition with such variable etiology and course.

The trials with Torecan have been too limited and too recent to give any assurance of freedom from the typical toxic symptoms generally associated with phenothiazines. While no reports of toxic reactions in the kidneys, liver, hematopoietic system or skin have thus far appeared, extrapyramidal effects have been noted. In the absence of proof of superior effectiveness and safety, Medical Letter consultants do not recommend the use of Torecan.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 305 E. 45th St., New York 17. Second-class postage paid at New York, and at Marion, Ohio. Subscription: 1 yr., $12.50; 2 yrs., $23; 3 yrs., $34 ($6.25 per year for residents, interns, students).